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The impact of specific HIV treatment-related adverse events on adherence to antiretroviral therapy: A systematic review and meta-analysis

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Poor adherence to antiretroviral therapies (ARTs) in human immunodeficiency virus (HIV)-infected patients increases the risk of incomplete viral suppression, development of viral resistance, progression to acquired immune deficiency syndrome and death. This study assesses the impact of specific treatment-related adverse events (AEs) on adherence to ART in the adult HIV patient population. A systematic review of studies involving adult HIV-infected patients aged ≥ 16 years that reported an odds ratio (OR) for factors affecting adherence to ART was conducted through a search of the EMBASE® and Medline® databases. Database searches were complemented with a search of titles in the bibliographies of review papers. Studies conducted in populations limited to a particular demographic characteristic or behavioural risk were excluded. To qualify for inclusion into a meta-analysis, treatment-related AEs had to be defined similarly across studies. Also, multiple ORs from the same study were included where study sub-groups were distinct. Random effects models were used to pool ORs. In total, 19 studies and 18 ART-related AEs were included in meta-analyses. Adherence to ART was significantly lower in patients with non-specific AEs than in patients who did not experience AEs [OR = 0.623; 95% confidence interval (CI): 0.465–0.834]. Patients with specific AEs such as fatigue (OR = 0.631; 95% CI: 0.433–0.918), confusion (OR = 0.349; 95% CI: 0.184–0.661), taste disturbances (OR = 0.485; 95% CI: 0.303–0.775) and nausea (OR = 0.574; 95% CI: 0.427–0.772) were significantly less likely to adhere to ART compared to patients without these AEs. Knowledge of specific treatment-related AEs may allow for targeted management of these events and a careful consideration of well-tolerated treatment regimens to improve ART adherence and clinical outcomes.

Keywords: antiretroviral therapy; adherence; adverse events; HIV

Introduction

Adherence to therapy can be considered as the extent to which a patient's medication-taking behaviour corresponds to the recommendations made by their healthcare provider (World Health Organisation [WHO], 2003). However, there is no standard method for measuring adherence in the scientific literature. This is evident in the variety of measures and thresholds employed in studies of adherence.

Poor adherence to medication can have serious consequences. Among human immunodeficiency virus (HIV)-infected patients, lack of adherence to combination antiretroviral therapies (ART) represents a particular concern since there are implications for individual patients as well as wider public health concerns (Wainberg & Friedland, 1998; WHO, 2003). At the patient level, non-adherence to ART can compromise HIV-related outcomes such as viral load, cluster of differentiation 4 (CD4) cell count, progression to acquired immune deficiency syndrome (AIDS) and survival (Bangsberg et al., 2001; Berg et al., 2005; de Olalla et al., 2002). In addition, non-adherence to ART may increase viral resistance to antiretroviral drugs and transmission of drug-resistant strains of HIV (Bangsberg et al., 2006; Sethi, Celentano, Gange, Moore, & Gallant, 2003; Wainberg & Friedland, 1998).

Despite the recent breakthroughs in HIV treatment, non-adherence remains a barrier to the improvement of disease outcomes for HIV-infected patients (World Health Organisation [WHO], 2010). Adherence to HIV medications is generally poor or falls below the levels required to optimise treatment efficacy. Vreeman, Wiehe, Pearce, and Nyandiko (2008) conducted a systematic review of paediatric adherence to HIV ART and found that the majority of included studies (76%) from low- and middle-income countries reported adherence levels of more than 75%, while another systematic review by Simoni et al. (2007) found that the majority of studies (60%) in high-income countries reported paediatric adherence levels of less than 75%. In addition, Mills et al. (2006) reported pooled estimates of 77% of sub-Saharan African patients and 55% of North

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American patients achieving threshold measurements of adherence as defined in the included studies.

There are numerous factors that may have a negative impact on adherence, including ART-related adverse events (AEs). Treatment-related AEs include temporary events such as nausea, vomiting and diarrhoea, as well as events of a longer duration such as lipodystrophy (Chesney, 2003). In a recent review, 31% of abstracts and 55% of full-text papers reported a relationship between ART-related AEs and adherence to treatment (Fogarty et al., 2002). Furthermore, in a French cohort of patients with HIV, treatment-related AEs were found to be the most potent predictors of discontinuation of ART (Duran et al., 2001). In the study by Duran et al. (2001), every additional AE experienced by patients increased the odds of non-adherence by 1.13 [95% confidence interval (CI): 1.03–1.24].

To date, only three published systematic reviews have assessed the extent to which ART-related AEs influence adherence to therapy (Atkinson & Petrozzino, 2009; Fogarty et al., 2002; Mills et al., 2006). However, these systematic reviews did not examine or quantify the effects of specific AEs. As such, there is a need for an improved understanding of the specific HIV treatment-related AEs that influence adherence. This knowledge will inform the development of safer therapies, thereby increasing the clinical effectiveness of ART and improving health outcomes. This systematic review was conducted to identify and synthesise quantitative evidence pertaining to the impact of safety and tolerability of ART and related AEs on adherence to treatment in HIV-infected populations.

Methods

This review used a systematic methodology to answer the following question: what are the treatment-related safety and tolerability determinants of adherence to oral antiretroviral medications in adult HIV patients?

Search strategies

The MEDLINE® and Embase® databases were searched for studies published through August 2010 without restriction to the earliest publication date. Searches were conducted using a broad search strategy that included keywords and medical subject heading terms for an adherence facet and an oral prescription medication facet (available upon request). The search was comprehensive and inclusive, designed to capture studies reporting determinants of adherence irrespective of disease area. Citations were then filtered to include only studies in HIV. In addition to database searches, bibliographies of identified systematic reviews were hand-searched to retrieve studies not captured by the initial database search.

Article selection and data extraction

Only studies published in English were considered for this review. Given the advancement in HIV treatment since the introduction of highly active antiretroviral therapy (HAART) in 1996, studies conducted prior to this date were excluded. No restrictions were placed on study design (with the exception that qualitative studies were not included), study duration, sample size, definition of adherence or methods used to measure adherence.

The study population of interest was adults with HIV infection irrespective of viral load, clinical status or prior treatment experience. Studies of adults aged ≥ 16 years, of any ethnicity or gender, were included if subjects were prescribed oral ART medication in an outpatient setting. Studies conducted exclusively in populations of specialised risk or demographic groups were excluded from the analysis. These populations included substance abusers, homeless individuals, institutionalised patients, military personnel, transgender individuals, victims of sexual abuse, one gender only or one race/ethnicity only.

Two independent reviewers assessed the titles and abstracts of each citation identified for potential inclusion according to the eligibility criteria outlined above. Full-text copies of candidate studies were ordered allowing the eligibility criteria to be applied to complete articles. Discrepancies in decisions at both screening stages were reconciled by a third independent reviewer.

Data from included studies were extracted by a single reviewer into a pre-designed Microsoft Access® database. A second reviewer checked extracted data with discrepancies resolved through consensus between the first and second reviewers. To avoid double-counting of patients, multiple publications considering the same population or dataset were considered as a single extraction. Extracted data included details of study design, population characteristics, definition of adherence, method of measuring adherence, therapy details, determinant variables and point estimates for adherence.

ART-related determinants of adherence were included in the analysis according to availability of data, that is, only treatment-related AEs reported in the included studies were considered. Determinant variables had to be comparable and defined in a similar way across studies prior to pooling in a meta-analysis. Furthermore, only studies that reported adjusted ORs

on the relationship between health outcomes and adherence/non-adherence were included in the meta-analyses. ORs were reversed if reported for odds of non-adherence. Multiple estimates from a single study for the same determinant were included if the estimates were derived from mutually exclusive sub-groups.

Statistical methods

For the purpose of this review, HIV treatment-related AEs were grouped into four sub-domains: general, mental health, sensory and gastrointestinal. Within each sub-domain, a separate meta-analysis was conducted to pool data from studies reporting ORs for the same determinant. Pooled estimates were calculated using conventional random effects meta-analysis techniques. STATA® (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP) was used to conduct meta-analyses, employing the *metan* command. Study outcomes were pooled using the DerSimonian and Laird random effects methodology and were weighted by inverse variance.

Results were presented as mean OR, CI and the heterogeneity index (I^2) for each determinant variable. In general, when interpreting heterogeneity between studies, an I^2 value above 50% is indicative of substantial heterogeneity and above 75% demonstrates considerable heterogeneity (Deeks, Higgins, & Altman, 2008). However, it is important to note that thresholds for the interpretation of I^2 can be misleading, since the value depends on several factors such as study design, size of effect estimates and significance levels. Furthermore, these thresholds are more applicable to interventional study designs whereas the majority of studies included in this review were observational in nature.

Results

Database searches for the original review yielded 18,641 references, with bibliographic searches of relevant reviews identifying 337 citations. Of these 18,978 citations, 219 studies met the inclusion criteria, of which, 19 studies were suitable for pooling in meta-analyses. The flow of citations through the review is illustrated in Figure 1. The majority of the 19 included studies were cross-sectional ($n = 14$), three were cohort studies and two were clinical trials. The included studies assessed adherence from a patient recall period that ranged from 1 day to 6 months and a few studies used multiple measurements. Study characteristics for studies included in the meta-analyses are detailed in Table 1.

Sub-domain 1: General AEs

Although non-specific AEs were found to be the most influential determinant of adherence to ART in this sub-domain (Figure 2), the utility of this result is limited given that the measured variable was indistinct. Differences in the categorisation and definition of AEs within this non-specific category could have contributed to the substantial heterogeneity observed between meta-analysed studies ($I^2 = 72.8\%$, $p < 0.0001$).

The most influential specific AE in this sub-domain was fatigue. Patients experiencing fatigue as a result of ART were significantly less likely to adhere to treatment than those who did not experience it. Patients with cough also had significantly decreased adherence to ART medications. Sexual dysfunction and lipodystrophy (abnormal fat distribution or accumulation) were each shown to reduce adherence to ART, however, these effects were not statistically significant (both $p > 0.05$). Dermatological conditions (rash, dry or itchy skin) did not appear to decrease adherence to HIV medications.

Sub-domain 2: Mental health AEs

Within the mental health sub-domain, confusion had the strongest effect on adherence. Individuals who experienced confusion had significantly lower odds of adherence than those who did not (Figure 3). The heterogeneity measure for this estimate was low and non-significant ($I^2 = 25.9\%$; $p = 0.245$) indicating little between study variation and good comparability of pooled populations. Patients with anxiety were also significantly less likely to adhere to ART medications. Insomnia appeared to decrease adherence to ART medications, however, the effect was not statistically significant.

Sub-domain 3: Sensory AEs

Experiencing taste disturbances significantly decreased adherence to ART compared to not experiencing this outcome (Figure 4). The pooled estimate for taste disturbances had low and non-significant heterogeneity ($I^2 = 21.9\%$; $p = 0.279$). Numbness did not appear to decrease adherence to ART. Pain when swallowing and tingling in mouth and tongue appeared to decrease adherence; however, neither AE was statistically significant (both $p > 0.05$).

Sub-domain 4: Gastrointestinal AEs

The most influential determinant of adherence to HIV treatment in this sub-domain was nausea (Figure 5). Heterogeneity across studies pooled in
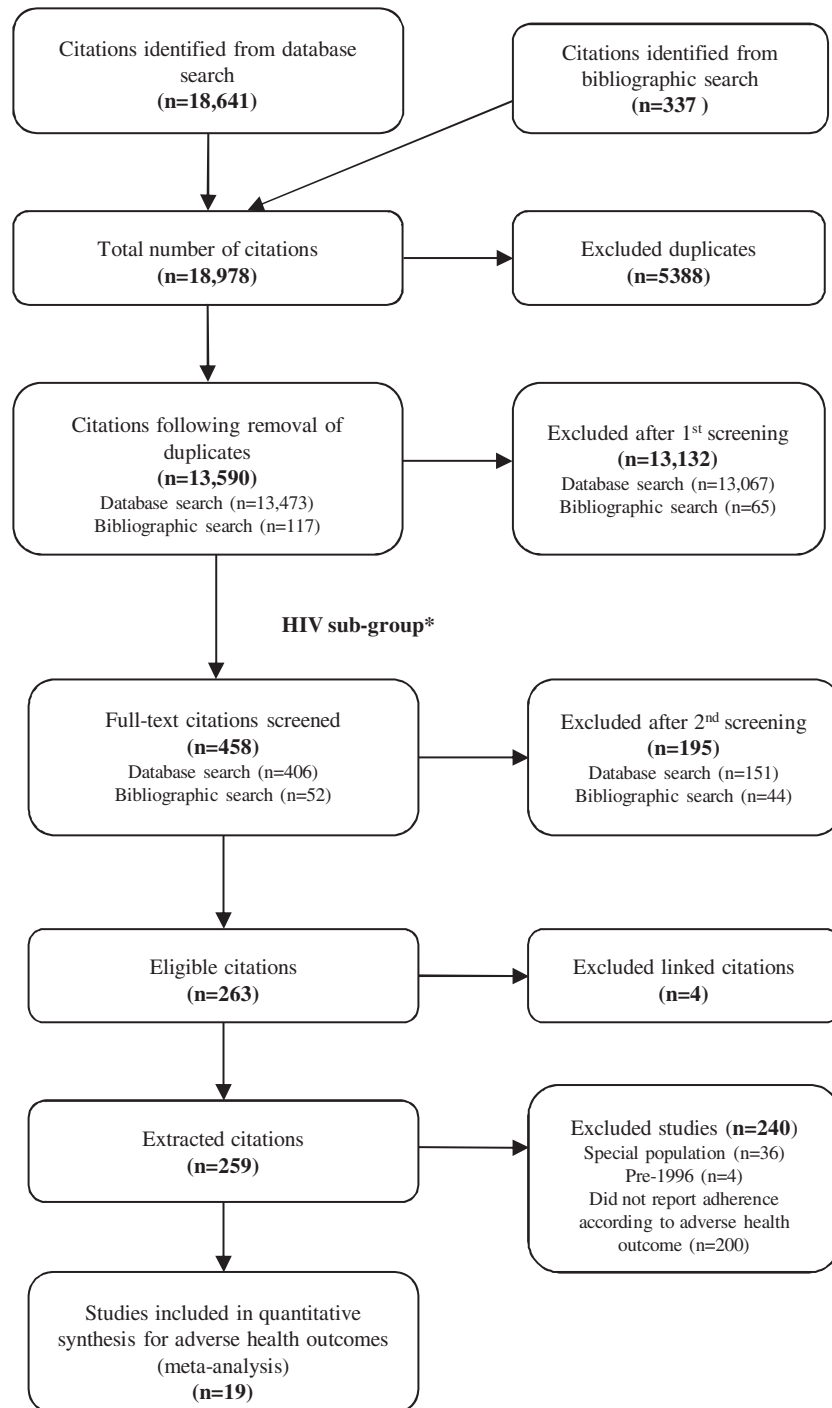
Figure 1. Flow of citations through the screening process. *The population of interest was originally patients with chronic diseases; this was later restricted to patients with HIV.

this meta-analysis was low and non-significant ($I^2 = 36.6\%$; $p = 0.163$). Patients with loss of appetite also had significantly decreased adherence. Other ART-related gastrointestinal AEs including abdominal pain, vomiting and diarrhoea were associated with lower adherence to ART; however, their effects were not statistically significant (all $p > 0.05$).

Discussion

This review provides the first set of meta-analyses focused on quantifying the effects of specific AEs on oral medication adherence in the treatment of HIV. Generally, ART-related AEs were found to decrease adherence, a finding corroborated by a previous meta-analysis that pooled studies reporting the effect

Table 1. Characteristics of studies included in the meta-analysis.

Study	N	Study design	Follow-up period	Medications used	Country	Adherence definitions/ assessment	Adherence recall period	Population characteristics	Determinant analysed
Aloisi et al. (2002)	366	Cohort	1 year	ART	Italy	• Self-reported questionnaire	6 months	• ICoNA cohort • Patients with HIV • Aged ≥ 18 years • At different stages of HIV disease • Treatment-naïve (receiving combination ART for ≥ 1 month) • Cohort at 1 year follow-up from inclusion in cohort	• Non-specific
Ammassari et al. (2001)	358	Cohort	NR	HAART	Italy	• Self-reported • Adherence defined as not having missed any HAART dose during the assessment period	3 days	• AdICoNA cohort • Receiving therapy for ≥ 1 month between May 1999 and March 2000 • Exclusion criteria were inability to complete the questionnaire, delirium or dementia and hospitalisation	• Lipodystrophy • Anxiety • Confusion • Insomnia • Nausea • Taste disturbances
Byakika-Tusiime et al. (2005)	304	Cross-sectional	N/A	• PI (indinavir, ritonavir, saquinavir, nelfinavir, lopinavir) • NNRTI (efavirenz, nevirapine, delavirdine) • NRTI (stavudine, lamivudine, didanosine, abacavir, zidovudine)	Uganda	• Self-reported • Adherence measured as the ratio of the doses reported to have been taken over the total number of doses prescribed • Adherence defined as >95% adherence to doses	3 days	• Patients with HIV • Aged ≥ 18 years • Receiving ART for ≥ 1 month	• Non-specific
da Silveira, Drachler, Leite, and Pinheiro (2003)	194	Cross-sectional	N/A	ART	Brazil	• Self-reported • Over two occasions (interval of approximately 1 month) • Arithmetic mean of two instances of 48 hours (first and second interview – doses that the patient reported taking divided by the number of doses prescribed over 4 days) • Adherence defined as >95% adherence to doses	Two occasions of 48-hour duration (i.e., 4 days total)	• Patients with HIV • Adolescent and adult patients who received ART from January 1998 to September 2000	• Non-specific

Table 1 (*Continued*)

Study	N	Study design	Follow-up period	Medications used	Country	Adherence definitions/ assessment	Adherence recall period	Population characteristics	Determinant analysed
Heath, Singer, Shaughnessy, Montaner and Hogg (2002)	638	Cross-sectional	N/A	Antiretroviral medications	Canada	• Self-reported • Intentional non-adherence defined as reporting either skipping or altering dosages of selective regimen components or temporary cessation of therapy that was not recommended by the physician in response to adverse drug effects	Past year	• Patients with HIV/AIDS • Participating in a drug treatment programme • Respondents to the annual participant survey	• Non-specific
Ickovics et al. (2002)	93	Cohort from an RCT	24 weeks	HAART (NRTI, NNRTI, PI)	US	• Self-reported • Reported missed/skipped doses over 4 days prior to visits (conducted every 4 weeks) up to week 24 • Adherence calculated by number of pills skipped over the number of pills prescribed • Adherence defined as >95% adherence to doses	4 days (every 4 weeks)	• AACTG 370 was a rollover study from an initial cohort from the AACTG 306 RCT • Successfully completed ≥48 weeks of treatment in AACTG 306 and remained on assigned study medication • Individuals aged >12 years with documented HIV-1 infection	• Non-specific
Johnson et al. (2003)	2765	Cross-sectional	N/A	ART	US	• Self-reported • Patients indicated how many antiretroviral pills they had skipped during the assessment period • Adherence calculated by number of pills actually taken divided by number of pills prescribed • Adherence defined as >90% adherence to doses	3 days	• Adult patients with HIV from four cities (San Francisco, Los Angeles, New York and Milwaukee) • Free of severe neuropsychological impairment or psychosis • Not involved in another behavioural intervention study related to HIV	• Non-specific

Table 1 (*Continued*)

Study	N	Study design	Follow-up period	Medications used	Country	Adherence definitions/ assessment	Adherence recall period	Population characteristics	Determinant analysed
Johnson et al. (2005)	2765	Cross-sectional	N/A	ART	US	● Self-reported ● Adherence was calculated based on number of pills taken divided by the number of pills respondents reported being expected to take ● Adherence defined as ≥ 90% adherence to doses	3 days	● Adult patients with HIV from four cities (San Francisco, Los Angeles, New York and Milwaukee) ● Screened for Healthy Living Project ● Free of severe neuropsychological impairment or psychosis ● Not currently involved in another behavioural intervention study related to HIV	● Cough ● Dermatological ● Fatigue ● Lipodystrophy ● Sexual dysfunction ● Anxiety ● Insomnia ● Numbness ● Diarrhoea ● Loss of appetite ● Nausea ● Vomiting
Murphy, Marelich, Huffman, and Steers (2004)	129	Cross-sectional	N/A	HAART	US	● Self-reported ● Three measures of adherence over three assessment periods ● Adherence assessed by asking participants how often they took their medications within the past time period on a 5-point response scale (for month-long adherence) or a 6-point response scale (for week-long/3-day adherence) ● Participants were adherent if they reported taking their medication "all of the time" or "most of the time" (month-long adherence); or if they had not missed any medications in the past week/3-day period	3 days, 1 week, 1 month	● Patients diagnosed with HIV/AIDS ● Prescribed HAART ● CD4 count ≥ 100 ● No opportunistic infections occurring 1 month prior to enrolment ● No participation in any other medication adherence study ● No current participation in a clinical trial ● No psychiatric condition such as florid psychosis or uncontrollable paranoid delusions	● Dermatological ● Numbness

Table 1 (*Continued*)

Study	N	Study design	Follow-up period	Medications used	Country	Adherence definitions/assessment	Adherence recall period	Population characteristics	Determinant analysed
Nieuwkerk, Gisolf, Sprangers, and Danner (2001)	160	Clinical trial	48 weeks	Ritonavir, saquinavir, stavudine	Netherlands, Belgium	• Self-reported • Patients were asked how many days they had taken all antiretroviral medication, how many days they had taken it more than 2 hours from time schedule, and how many days they had taken ritonavir/saquinavir together with food or after a meal	4 weeks	• Prometheus study • Patients with HIV-1	• Pain when swallowing • Taste disturbances • Tingling in mouth and tongue • Loss of appetite • Abdominal pain • Diarrhoea • Nausea • Vomiting
Pinheiro, De Carvalho-Leite, Drachler, and Silveira (2002)	195	Cross-sectional	N/A	Antiretroviral medications	Brazil	• Self-reported • Number of pills taken divided by the number of pills prescribed over the assessment period	48 hours	• Patients with HIV • Aged 17 years to 67 years • Initiated ART	• Non-specific
Remien et al. (2007)	200	Cross-sectional	N/A	ART	Brazil	• Self-reported • Adherence was based on number of missed/skipped pills during the assessment period divided by the number of pills respondents reported being expected to take	3 days	• Patients with HIV/AIDS • Recruited from two large teaching hospitals and several NGOs where HIV-positive adults receive supportive services in Rio de Janeiro	• Loss of appetite
Sarma et al. (2008)	310	Cross-sectional	N/A	Stavudine, lamivudine, nevirapine, zidovudine efavirenz, other NRTI/NNRTI combination regimens (abacavir, didanosine)	India	• Self-reported • Mean 4-day adherence was calculated by dividing the number of pills actually taken by the number of pills needed to be taken for 4 days as a percentage • Adherence defined as >90% adherence to doses	4 days	• Patients with HIV • Aged ≥ 18 years • Receiving ART for ≥ 30 days between May 2004 and August 2004	• Non-specific

Table 1 (*Continued*)

Study	N	Study design	Follow-up period	Medications used	Country	Adherence definitions/assessment	Adherence recall period	Population characteristics	Determinant analysed
Shah et al. (2007)	279	Cross-sectional	N/A	ART (NNRTI, NRTI, PI)	India	• Self-reported • Patients were considered adherent if they had taken ≥ 95% of planned doses over the assessment period	4 days	• Patients with HIV • Aged ≥ 18 years • Receiving ART for ≥ 3 months from December 2004 to April 2005 • Patients with acute illness or unaware of their HIV infection status were excluded	• Non-specific
Tadios and Davey (2006)	431	Cross-sectional	N/A	HAART	Ethiopia	• Self-reported • Patients were considered adherent if they had taken ≥ 95% of therapy correctly over the assessment period	1 week	• Adult patients with HIV/AIDS attending three ART centres in Addis Ababa from December 2004 to January 2005	• Non-specific
Tessema et al. (2010)	504	Cross-sectional	N/A	HAART	Ethiopia	• Respondents were asked whether they had missed any doses the day prior to completing the questionnaire, and how often doses were missed in general (every day to never) • Respondents who reported that they had not forgotten a dose the day prior to the completion of the questionnaire and those that responded as never forgetting doses were categorised as adherent	1 day	• Adult outpatients with HIV/AIDS who were receiving ART for ≥ 3 months	• Non-specific
Trotta et al. (2003)	596	Cohort	1 year	PI-containing regimen and nevirapine-containing HAART regimen	Italy	• Self-reported • 16-item self-administered questionnaire • Non-adherence defined as reporting to have missed ≥ 1 dose or having ever experienced an interruption in drug supply during the assessment period	1 week	• Patients with HIV • Receiving ART for ≥ 1 month • Patients with dementia of grade two or greater or hospitalisation at enrolment were excluded	• Cough • Dermatological • Fatigue • Lipodystrophy • Sexual dysfunction • Anxiety • Confusion • Nausea • Vomiting

Table 1 (*Continued*)

Study	N	Study design	Follow-up period	Medications used	Country	Adherence definitions/ assessment	Adherence recall period	Population characteristics	Determinant analysed
Wang et al. (2008)	308	Cohort	NR	ART (NNRTI, NRTI)	China	• Self-reported • Number of doses taken in the assessment period prior to interview • Adherence defined as >90% of doses taken correctly in previous week	7 days	• Patients with HIV • Returning for monthly ART follow-up at selected study sites between April 2006 and July 2006	• Dermatological
Wilson, Doxa-nakis and Fairley (2004)	200	Cross-sectional (observational)	28 days	ART	Australia	• Adherence was measured using the "every visit adherence questionnaire" • Percentage self-reported adherence was calculated for 4 days, 7 days and 28 days by dividing the number of doses missed in a period of time by the number of prescribed doses for that period and multiplying by 100, then subtracting this figure from 100 • Non-adherence defined as <98.2% adherence to doses	4 days, 7 days and 28 days	• Participants were recruited from the study site between October 2002 and February 2003, if they were aged ≥18 years, HIV-positive, and currently using ART	• Non-specific

Note: AACTG, Adult AIDS Clinical Trial Group; AdICoNA, Adherence Italian Cohort of Antiretroviral-Naïve patients; AIDS, acquired immune deficiency syndrome; ART, antiretroviral therapy; CD4, cluster of differentiation 4; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; ICoNA, Italian Cohort of Antiretroviral-Naïve patients; NGO, non-governmental organisation; N/A, not applicable; NR, not reported; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RCT, randomised controlled trial; US: United States.

Adverse event	Pooled OR (95% CI)	*P* value (OR)	I^2 (%)	No. of included studies
Cough	0.65 (0.53, 0.79)	<0.001	0.00	2
Dermatological	0.96 (0.61, 1.52)	0.876	62.40	4
Fatigue	0.63 (0.43, 0.92)	0.016	52.80	2
Lipodystrophy	0.74 (0.43, 1.26)	0.270	72.80	3
Non-specific*	0.62 (0.46, 0.83)	0.001	72.80	12
Sexual dysfunction*	0.72 (0.17, 2.96)	0.647	78.40	2

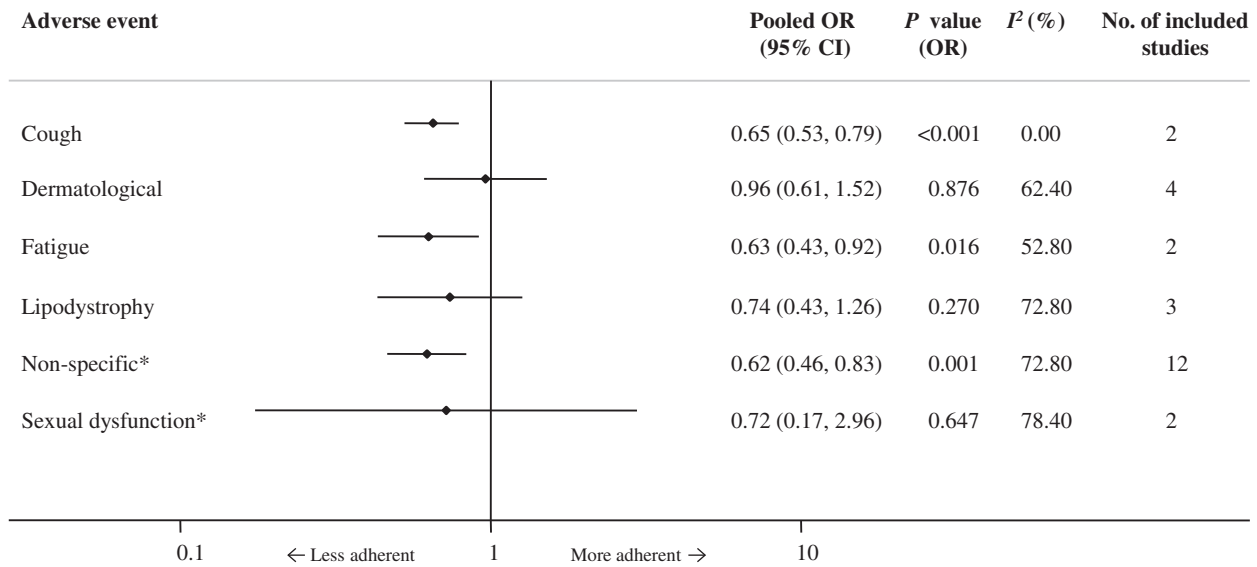0.1   ← Less adherent   1   More adherent →   10

Figure 2. Forest plot of meta-analyses of ORs pertaining to the effects of treatment-related general AEs on adherence. Each OR represents a pooled estimate for the corresponding adverse health outcome. All meta-analyses were conducted using a random effects model. *This OR was calculated using multiple studies and data from mutually-exclusive sub-groups within the same study. CI, confidence interval; I^2, heterogeneity index; OR, odds ratio.

of AEs on HIV medication adherence (Atkinson & Petrozzino, 2009). However, the previous study did not differentiate between various AEs and reported them as an amalgamated determinant of adherence. Therefore, it was unclear which AEs had the highest impact on adherence. In contrast, the present work demonstrated that the effect magnitude varied between specific AEs and not all events were found to have a statistically significant influence on adherence.

The findings of this review are supported by previous studies reporting on the impact of HIV treatment-related AEs. In the Italian Cohort of Anti-retroviral-Naïve Patients, 21.1% of participants dis-

continued combination ART due to treatment toxicity over a median follow-up period of 45 weeks, whereas only 5.1% of participants in the same population discontinued therapy due to treatment failure (Mocroft et al., 2001; Monforte et al., 2000). Moreover, a study conducted by Stone et al. (2001) in the HIV Epidemiology Research cohort, indicated that patients who reported having two or more adverse reactions to ART were more likely to discontinue treatment than patients who did not experience these reactions.

The treatment-related AEs included within this research were only those reported in studies that met the systematic review inclusion criteria. Therefore,

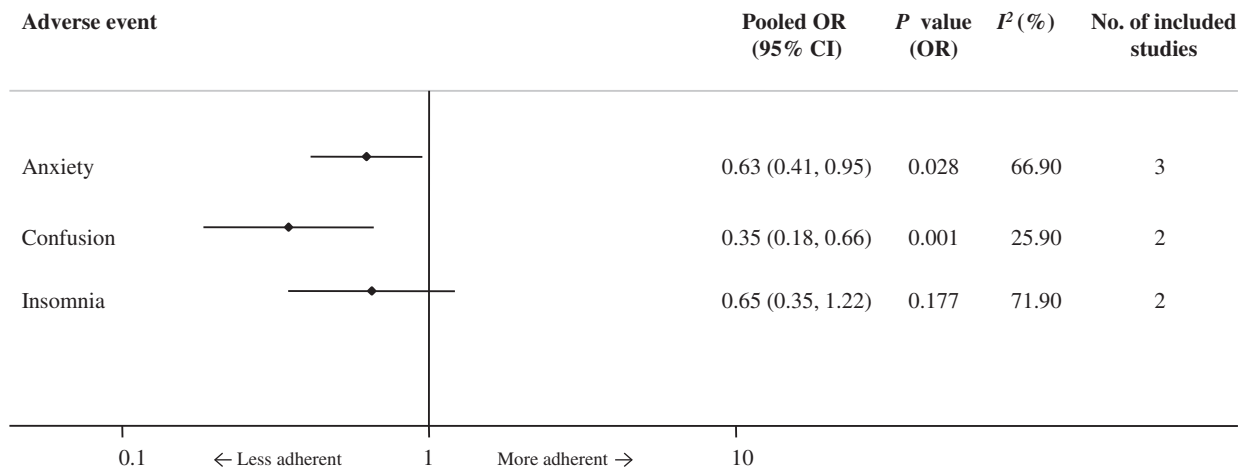| Adverse event	Pooled OR (95% CI)	*P* value (OR)	I^2 (%)	No. of included studies
Anxiety	0.63 (0.41, 0.95)	0.028	66.90	3
Confusion	0.35 (0.18, 0.66)	0.001	25.90	2
Insomnia	0.65 (0.35, 1.22)	0.177	71.90	2

0.1   ← Less adherent   1   More adherent →   10

Figure 3. Forest plot of meta-analyses of ORs pertaining to the effects of treatment-related mental health AEs on adherence. Each OR represents a pooled estimate for the corresponding adverse health outcome. All meta-analyses were conducted using a random effects model. CI, confidence interval; I^2, heterogeneity index; OR, odds ratio.

Adverse event	Pooled OR (95% CI)	*P* value (OR)	*I²*(%)	No. of included studies
Numbness*	0.92 (0.64, 1.32)	0.665	70.20	2
Pain when swallowing‡	0.50 (0.16, 1.56)	0.231	44.90	1
Taste disturbances*	0.49 (0.30, 0.77)	0.003	21.90	2
Tingling in mouth and tongue‡	0.67 (0.42, 1.05)	0.079	25.30	1

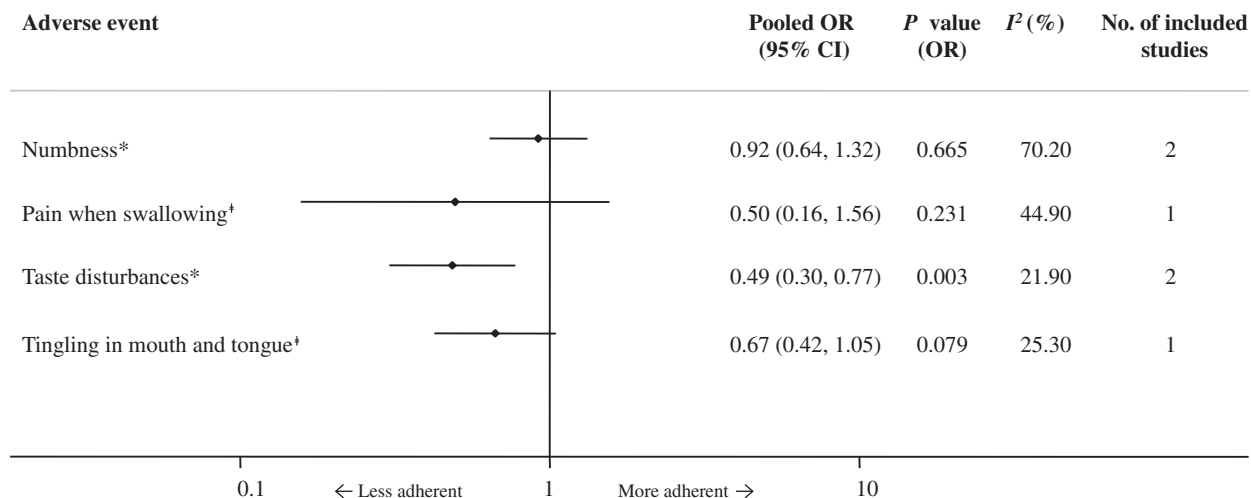0.1   ← Less adherent   1   More adherent →   10

Figure 4. Forest plot of meta-analyses of ORs pertaining to the effects of treatment-related sensory AEs on adherence. Each OR represents a pooled estimate for the corresponding adverse health outcome. All meta-analyses were conducted using a random effects model. *This OR was calculated using multiple studies and data from mutually-exclusive sub-groups within the same study. ‡This OR was derived from mutually-exclusive sub-groups in a single study. CI, confidence interval; *I²*, heterogeneity index; OR, odds ratio.

some symptoms that have been previously reported in patients with HIV, such as depression and neuropathy, were not included in this study. The specific AEs identified through this work as having significant negative implications for medication adherence included fatigue, cough, anxiety, confusion, taste disturbances, loss of appetite and nausea. Fatigue and anxiety have been previously identified as common symptoms in patients with HIV (not necessarily treatment-related) that negatively impact adherence (Duran et al., 2001; Tucker, Burnam, Sherbourne, Kung, & Gifford, 2003). In the context of combination ART regimens, confusion can be a major barrier to adherence since these regimens entail following detailed and complex recommendations pertaining to the timing, order and combinations of multiple medications (Ammassari et al., 2001). Taste disturbances, loss of appetite and nausea are also very

Adverse event	Pooled OR (95% CI)	*P* value (OR)	*I²*(%)	No. of included studies
Abdominal pain‡	0.49 (0.16, 1.57)	0.231	47.70	1
Diarrhoea*	0.94 (0.79, 1.11)	0.448	0.00	2
Loss of appetite*	0.54 (0.32, 0.93)	0.027	60.60	3
Nausea*	0.57 (0.43, 0.77)	<0.001	36.60	4
Vomiting*	0.49 (0.24, 1.02)	0.056	58.10	3

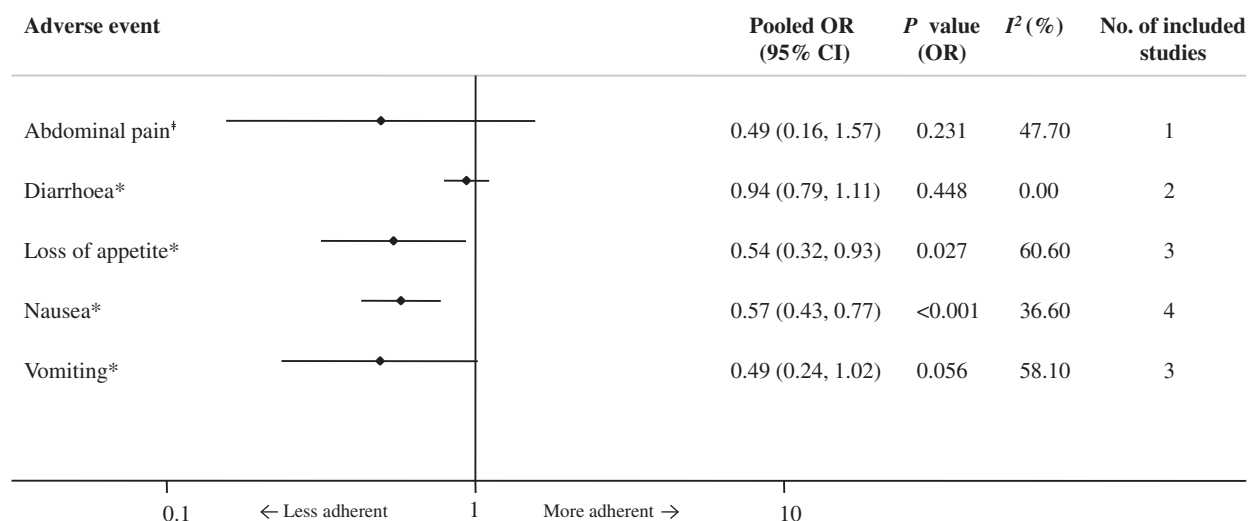0.1   ← Less adherent   1   More adherent →   10

Figure 5. Forest plot of meta-analyses of ORs pertaining to the effects of treatment-related gastrointestinal AEs on adherence. Each OR represents a pooled estimate for the corresponding adverse health outcome. All meta-analyses were conducted using a random effects model. *This OR was calculated using multiple studies and data from mutually-exclusive sub-groups within the same study. ‡This OR was derived from mutually-exclusive sub-groups in a single study. CI, confidence interval; *I²*, heterogeneity index; OR, odds ratio.

relevant to combination ART, as some regimens necessitate dietary requirements that may compound these AEs (Stone et al., 2001).

Certain findings relating to the effect of treatment-related AEs presented in the current review differ from those published previously. For instance, this study showed that diarrhoea did not significantly decrease adherence to ART despite being a common side effect reported by patients with HIV (Duran et al., 2001). The reason for this finding may be that the pooled OR for diarrhoea was calculated using point estimates that differed in the direction of association with adherence, thereby bringing the pooled OR closer to 1. Another interpretation is that since none of the ORs reported in the individual studies were statistically significant, it is possible that diarrhoea may not be a significant factor for non-adherence. Furthermore, this research showed that lipodystrophy did not significantly affect adherence, in contrast to a study showing self-reported lipodystrophy as an important reason for discontinuation of HIV medication (Kasper, Arboleda, & Halpern, 2000). Similarly, self-reported skin rashes were barriers to adherence in a previous study (Afolabi, Ijadunola, Fatusi, & Olasode, 2009), whereas dermatological conditions were not identified as an important barrier to adherence in the current study. Both Kasper et al. (2000) and Afolabi et al. (2009) assessed reasons for non-adherence that have been reported by patients directly and not determined through statistical analysis of reported determinants. This may explain why the findings of these two studies were different from those of the current review, which excluded self-reported reasons for adherence/non-adherence.

The assimilation of evidence from included studies and the utility of review findings have a number of limitations, the greatest of which was associated with the substantial variation in the measurement and definition of adherence and assessment of AEs across studies. For example, Johnson et al. (2005) asked participants directly whether they perceived AEs as being due to HIV medication, whereas Sarna et al. (2008) used the Adult AIDS Clinical Trial Group signs and symptoms questionnaire to derive side effects scores. The distinction made by patients between treatment-related AEs and disease-related symptoms is likely to vary and less adherent individuals may be more likely to attribute non-adherence to medication side effects. Moreover, patients may report AEs and adherence to therapy differently in various study settings. For example, three studies in this review implemented an interviewer-administered questionnaire to collect data (Byakika-Tusiime et al., 2005; da Silveira et al., 2003; Pinheiro et al., 2002). In such cases, adherent patients might have been more likely to attend clinics and appointments than non-adherent patients, potentially introducing biases to collected data.

The meta-analysis only included studies reporting adjusted ORs; however, individual studies may have adjusted for different factors, potentially increasing heterogeneity. Further, studies were conducted across a variety of geographies, where political or economic factors may influence the behaviour of patients, and there was substantial variation in the demographics of populations included in the meta-analysis. Factors contributing to demographic heterogeneity provide a valuable target for further investigation, as patient-related characteristics may also influence adherence to ART. Finally, temporal effects related to the period of adherence observation or the years in which included studies were conducted may have been influential given the advances made in HAART over time. However, a sensitivity assessment of findings from the meta-analyses based on study year was beyond the scope of this review.

In the course of this study, the authors observed that certain classes of ARTs were associated with certain AEs. For example, protease inhibitors were most frequently linked to lipodystrophy, fatigue, vomiting and diarrhoea (Byakika-Tusiime et al., 2005; Ickovics et al., 2002; Shah et al., 2007; Trotta et al., 2003), while nucleoside reverse transcriptase inhibitors were associated with fatigue, vomiting, diarrhoea and abdominal pain (Byakika-Tusiime et al., 2005; Ickovics et al., 2002). As for non-nucleoside reverse transcriptase inhibitors, mood disorders were most commonly observed (Byakika-Tusiime et al., 2005; Ickovics et al., 2002). It is difficult to attribute particular side effects to isolated drugs as combination drug therapy is the standard of care in this disease area and since numerous drug classes share common side effects. In addition, AEs may result from interactions between separate drugs used in the same combination therapy. For this reason, a subgroup analysis based on drug class was not considered.

Finally, it is noteworthy that poor adherence to ART medications may have wider public health consequences including the development of treatment-resistant strains of HIV and an increased burden of illness to society and healthcare systems. However, these issues were beyond the scope of this review.

Conclusion

This study has identified a variety of HIV medication-related barriers to adherence and provided pooled

estimates for the effects of specific AEs on treatment adherence. Findings from this work support the notion that managing HIV treatment-related AEs can improve medication adherence, and therefore, promote the optimisation of ART regimens to decrease viral resistance to therapy, patient progression to AIDS and patient mortality. In addition, patients should have a clear understanding of the risk of treatment-related AEs when initiating or changing HIV therapy and provide agreement on the most appropriate treatment. Furthermore, disease management programmes designed to educate patients on methods to minimise AEs and their impact could be expected to improve patients' adherence to prescribed therapy and, ultimately, clinical outcomes. Finally, future research should examine the interplay between patient characteristics, such as age, gender and race, and clinical characteristics, such as ARV side effects, pill burden and comorbidities, and their impact on adherence.

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